Fatalities Reported to FDA Following Blood Collection and Transfusion

Annual Summary for Fiscal Year 2012

I. Background

As previously mentioned in the annual summary of fatalities reported to the FDA in Fiscal Years (FY) 2005 through FY2011, the blood supply is safer today than at any time in history. Due to advances in donor screening, improved testing, automated data systems, and changes in transfusion medicine practices, the risks associated with blood transfusion continue to decrease. Overall, the number of transfusion related fatalities reported to the FDA remains small in comparison to the total number of transfusions. In 2008, for example, there were approximately 24 million blood components transfused.[1] During the proximate period of FY2008, there were 54 reported transfusion related and potentially[2] transfusion related fatalities, with subsequent reports of 66 in FY2009, 64 in FY2010, 58 in FY2011, and 65 in FY2012.

CBER is distributing this summary of transfusion fatality reports received by the FDA to make public the data received in FY2012, to provide the combined data received over the last five fiscal years, and to compare the FY2012 report to the fatality reports received in the previous four fiscal years.[3] We also include information on the infrequent reports of post-donation fatalities. Throughout this report we note changes over time, but the reader should interpret these changes cautiously, given the small numbers of reports and inherent variations in reporting accuracy. The significance of shifts in numbers derived from small populations may appear to be greater than they really are.

Refer to Sections 606.170(b) and 640.73 of Title 21, Code of Federal Regulations (21 CFR 606.170(b) and 21 CFR 640.73), for fatality reporting requirements. For information regarding the notification process, see our web page, Notification Process for Transfusion Related Fatalities and Donation Related Deaths, http://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/default.htm. For further information, see our *Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion*, September 2003.[4]

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[1] Report of the US Department of Health and Human Services. The 2009 national blood collection and utilization survey report. Washington, DC: US Department of Health and Human Services, Office of the Assistant Secretary of Health, 2011.

[2] Transfusion could not be ruled out as the cause of the fatality.

[3] The FY2005 - FY2007 data are not discussed in this report, but are available at: http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM129521.pdf

[4] Guidance for Industry: Notifying FDA of Fatalities Related to Blood Collection or Transfusion, September, 2003. http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/blood/ucm074947.htm.

A team of CBER medical officers reviews the documentation submitted by the reporting facilities and obtained by FDA investigators, to assess the relationship, if any, between the blood donation or transfusion and the reported fatality.

If you have questions concerning this summary, you may contact us using any of the three following options:

1. Email us at fatalities2@fda.hhs.gov,
2. Call us at 301-827-6220, or
3. Write us at:
   FDA/Center for Biologics Evaluation and Research
   Office of Compliance and Biologics Quality
   Division of Inspections and Surveillance (HFM-650)
   1401 Rockville Pike, Suite 200 North
   Rockville, Maryland 20852-1448

II. Results

During FY2012 (October 1, 2011, through September 30, 2012), we received a total of 88 fatality reports. Of these reports, 74 were transfusion recipient fatalities and 14 were post-donation fatalities.

Of the 74 transfusion recipient fatality reports, we concluded:

a) 38 (51%) of the fatalities were transfusion-related,
b) 27 (36%) of the fatalities were cases in which transfusion could not be ruled out as the cause of the fatality,
c) 9 (12%) of the fatalities were unrelated to the transfusion.

Of the 14 post-donation fatality reports, we concluded:

a) 11 of the fatalities were cases in which donation could not be ruled out as the cause of the fatality,
b) 3 of the fatalities were unrelated to the donation.

We summarize the results of our review in the following sections. Sections A through D of this document present the transfusion-related fatalities. Sections E and F and Table 4 present the fatality reports which were unrelated to the transfusion, or in which we could not rule out the transfusion as the cause of death. Section G presents the post-donation fatality reports.

G. Post-Donation Fatalities

A. Overall Comparison of Transfusion-Related Fatalities Reported from FY2008 through FY2012

In combined Fiscal Years 2008 through 2012, Transfusion Related Acute Lung Injury (TRALI) caused the highest number of reported fatalities (37%), followed by hemolytic transfusion reactions (total of 27%) due to non-ABO (16%) and ABO (11%) incompatibilities. Complications of Transfusion Associated Circulatory Overload (TACO) (18%), microbial infection (11%), and anaphylactic reactions (6%) each accounted for a smaller number of reported fatalities (Table 1 and Figure 1). The number of fatalities attributed to TACO has varied over the reporting period, with no noted trend. Recent articles provide additional information about TACO.[5,6,7] The number of reported transfusion related deaths attributable to anaphylaxis[8,9] has remained small over the last five fiscal years. With the exception of one FY2010 case, in which IgA levels were not measured, patient IgA deficiency was ruled out in 11 of the 12 cumulatively reported cases. In another FY2010 case, a haptoglobin deficiency was possibly implicated in the patient's anaphylactic reaction.

Table 1: Transfusion-Related Fatalities by Complication, FY2008 through FY2012

Complication	FY08	FY08	FY09	FY09	FY10	FY10	FY11	FY11	FY12	FY12	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
TRALI*	16	35%	13	30%	18	45%	10	33%	17	45%	74	37%
HTR (non-ABO)	7	15%	8	18%	5	13%	6	20%	5	13%	31	16%
HTR (ABO)	10	22%	4	9%	2	5%	3	10%	3	8%	22	11%
Microbial Infection	7	15%	5	11%	2	5%	4	13%	3	8%	21	11%
TACO	3	7%	12	27%	8	20%	4	13%	8	21%	35	18%
Anaphylaxis	3	7%	1	2%	4	10%	2	7%	2	5%	12	6%
Other	0	0%	1**	2%	1**	3%	1**	3%	0	0%	3	1%
Totals	46	100%	44	100%	40	100%	30	100%	38	100%	198	100%

*These numbers include both "TRALI" and "possible TRALI" cases[10,11]

**Other:

FY2009: Hypotensive Reaction[12]

[5] Murphy EL, Kwaan N, Looney MR, et al. Risk Factors and Outcomes in Transfusion-associated Circulatory Overload. http://dx.doi.org/1016/j.amjmed.2012.08.019.

[6] Narick C, Triulzi J, Yazer M. Transfusion-associated circulatory overload after plasma transfusion. Transfusion 2012;52:160-165.

[7] Tobian A, Sokoll L, Tisch D, et al. N-terminal pro-brain natriuretic peptide is a useful diagnostic marker for transfusion-associated circulatory overload. Transfusion 2008;48:1143-1150.

[8] Nara A, Aki T, et al. Death due to blood transfusion-induced anaphylactic shock: A case report. Legal Medicine 2010:12:148-150.

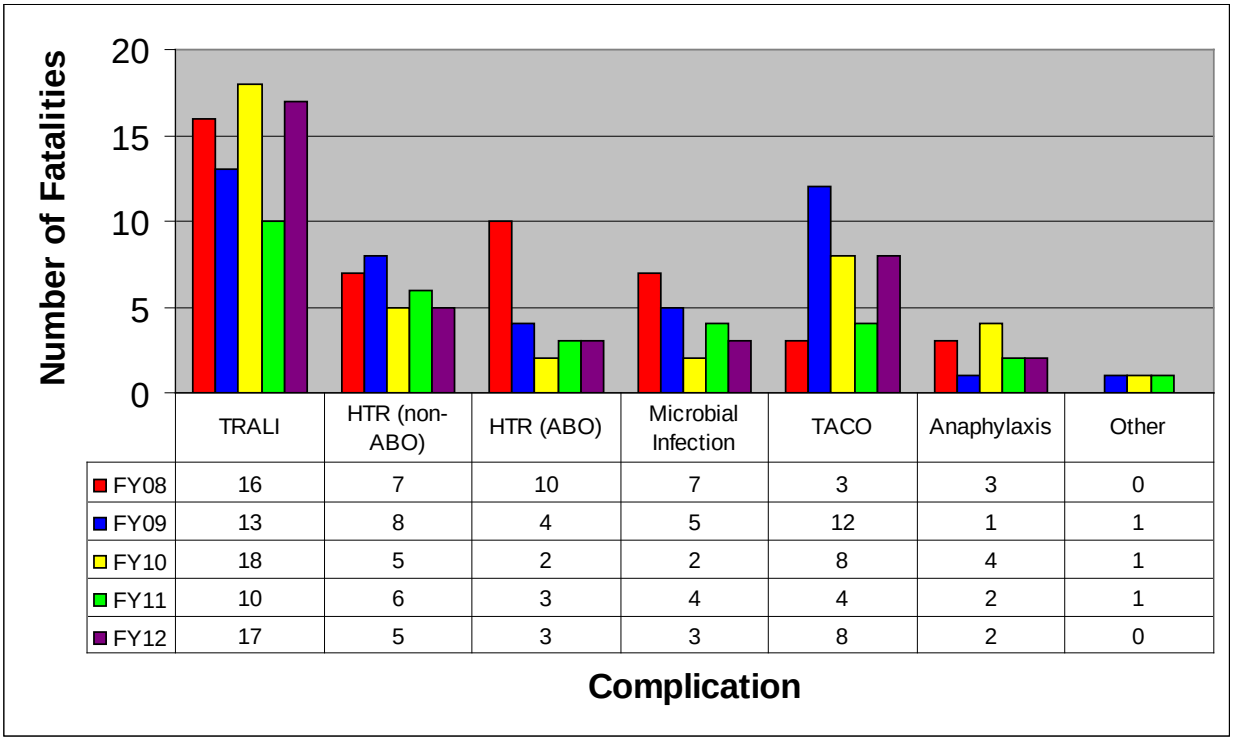
[9] Hirayama F. Current Understanding of allergic transfusion reactions: incidence, pathogenesis, laboratory tests, prevention and treatment. British Journal of Haematology 2013;160:434-444.

[10] Goldman M, Webert KE, Arnold DM, et al. Proceedings of a consensus conference: towards an understanding of TRALI. Transfus Med Rev 2005;19:2-31.

[11] Kleinman S, Caulfield T, Chan P, et al. Toward an understanding of transfusion-related acute lung injury: statement of a consensus panel. Transfusion 2004;44:1774-1789.

FY2010: Graft vs. Host Disease (GVHD)
FY2011: GVHD

Figure 1: Transfusion-Related Fatalities by Complication, FY2008 through FY2012



	TRALI	HTR (non-ABO)	HTR (ABO)	Microbial Infection	TACO	Anaphylaxis	Other
FY08	16	7	10	7	3	3	0
FY09	13	8	4	5	12	1	1
FY10	18	5	2	2	8	4	1
FY11	10	6	3	4	4	2	1
FY12	17	5	3	3	8	2	0

B. Transfusion Related Acute Lung Injury (TRALI)

TRALI represented 37% of confirmed transfusion related fatalities reported to CBER over the last five fiscal years. There was an increase in TRALI fatalities, from 10 (33% of confirmed transfusion related fatalities) in FY2011, to 17 (45%) in FY2012 (Table 1 and Figure 1). However, the TRALI fatalities in FY2008 (16/46 or 35%) represented a decrease from FY2007 when the number of confirmed transfusion-related TRALI fatalities was 34/52 or 65%. Following this decrease, the total number of TRALI fatalities, as well as the number of TRALI fatalities associated with plasma products, has remained relatively unchanged over the reporting period FY2008 - FY2012 (Figure 2 and Figure 3).

In FY2012, the 17 TRALI cases were temporally associated with products collected from 39 donors. Genders were identified for 30 of the donors, which included 18 males and 12 females. HLA/HNA antibody test results were available for 17 of these donors.

In four of the 17 FY2012 TRALI cases, reporters who included patient testing data were able to match donor antibodies with recipient cognate antigens.

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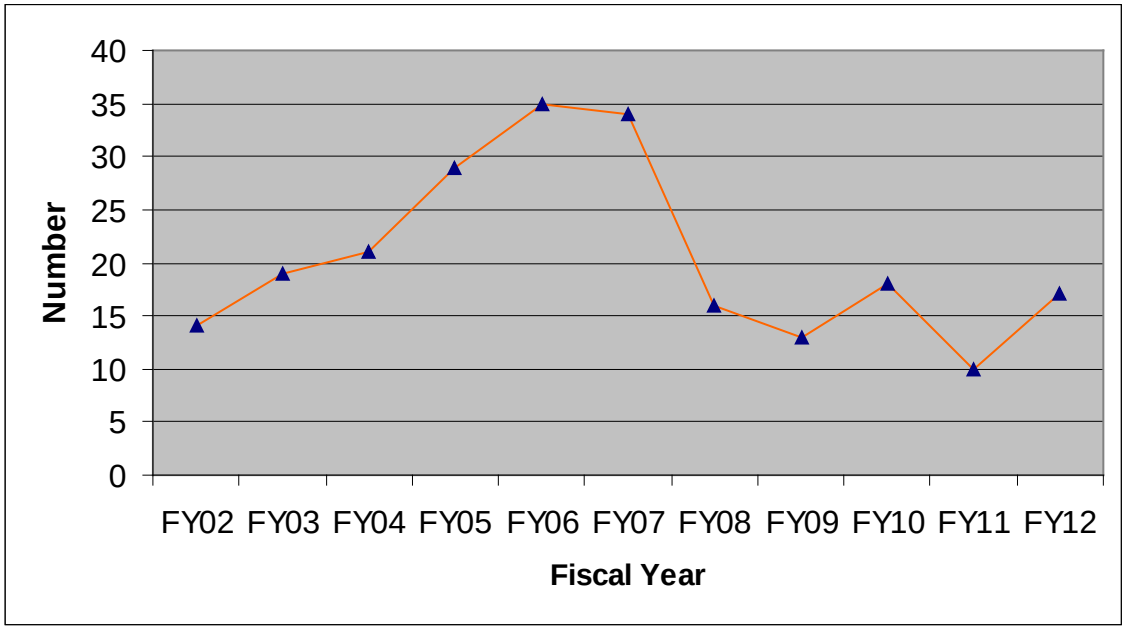
[12] Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Biovigilance Component protocol. 2009:17.

Our limited data do not elucidate the role of particular donor antibodies or donor gender in the etiology of the TRALI reactions.

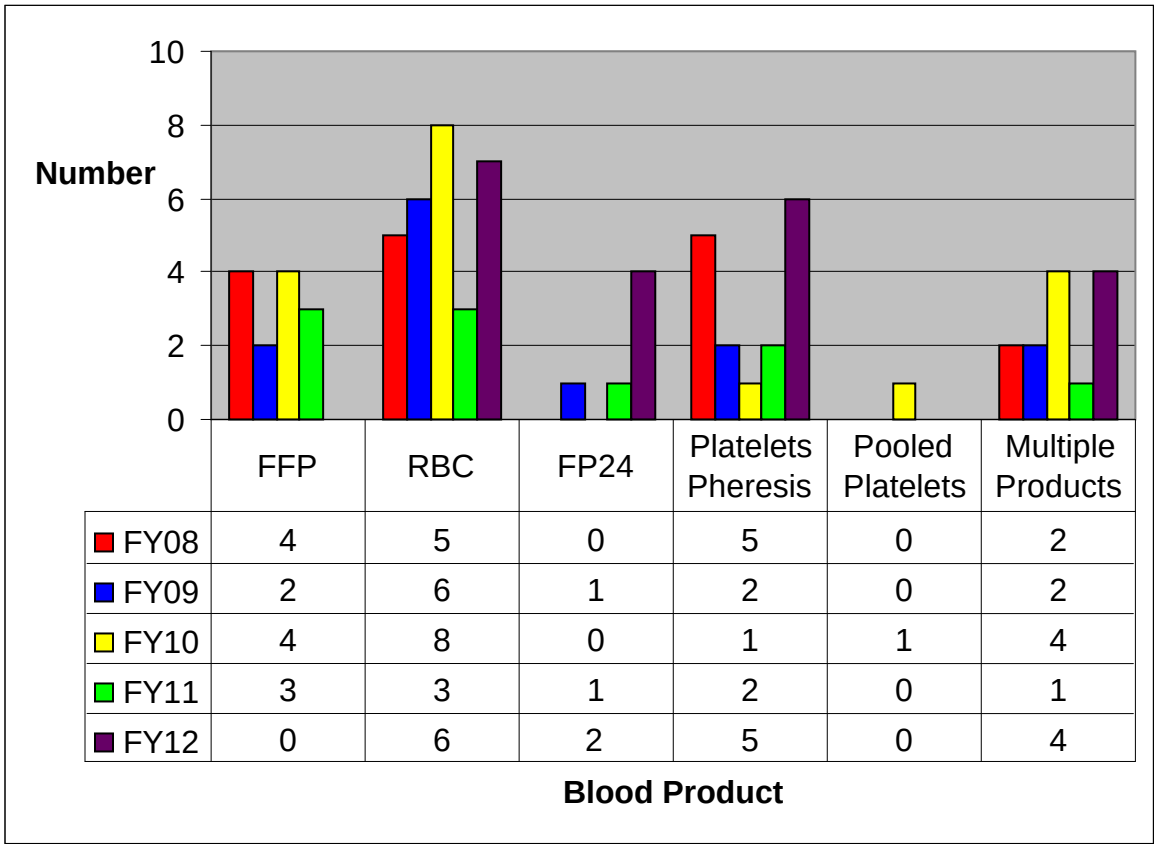
Although this complication of transfusion continues to be one of the leading causes of transfusion-related fatalities reported to the FDA, the voluntary measures taken by the transfusion community to reduce the risk of TRALI have coincided with a reduction in the number of TRALI deaths. Current literature describes the results of continued international efforts to reduce the use of plasma for transfusion prepared from female donors, and other strategies to reduce the incidence of TRALI.[13,14,15,16,17,18,19,20]

Figure 2: TRALI Cases, FY2002 through FY2012



[13] Muller MCA, Juffermans NP. Transfusion-related acute lung injury: a preventable syndrome? Expert Rev. Hematol. 2012;5(1):97-106.
[14] Wiersum-Osselton JC, Middleburg RA, Beckers EAM, et al. Male-only fresh frozen plasma for transfusion-related acute lung injury prevention: before-and-after comparative cohort study. Transfusion 2011;51:1278-1283.
[15] Schmidt AE, Adamski J. Pathology Consultation on Transfusion-Related Acute Lung Injury (TRALI). Am J Clin Pathol 2012;138:498-503..
[16] Saidenberg E, Petraszko T, et al. Transfusion-Related Acute Lung Injury (TRALI): A Canadian Blood Services Research and Development Symposium. Transfusion Medicine Reviews 2010;24:305-324.
[17] Arinsburg SA, Skerrett DL, Karp JK, et al. Conversion to low transfusion-related acute lung injury (TRALI)-risk plasma significantly reduces TRALI. Transfusion 2012;52:946-952.
[18] Reesink HW, Lee J, Keller A, et al. Measures to prevent transfusion-related acute lung injury (TRALI). Vox Sanguinis 2012;103:231-259.
[19] Toy P, Ognjen G, Bacchetti P, et al. Transfusion-related lung injury: incidence and risk factors. Blood 2012;119:1757-1767.
[20] Eder A, Herron Jr R, Strupp A, et al. Effective reduction of transfusion-related lung injury risk with male-predominant plasma strategy in the American Red Cross (2006-2008). Transfusion 2010;50:1732-1742.

Figure 3: Reports of TRALI Cases by Implicated Blood Product, FY2008 through FY2012



	FFP	RBC	FP24	Platelets Pheresis	Pooled Platelets	Multiple Products
FY08	4	5	0	5	0	2
FY09	2	6	1	2	0	2
FY10	4	8	0	1	1	4
FY11	3	3	1	2	0	1
FY12	0	6	2	5	0	4

C. Hemolytic Transfusion Reactions

In FY2012, the number of reported fatal hemolytic transfusion reactions was relatively unchanged in comparison to the number reported in FY2011 (Tables 1 and 2, and Figure 1). The downward trend in the total number of reported fatalities due to hemolytic transfusion reactions has continued since FY2001 (Figure 4).

Table 2: Hemolytic Transfusion Reactions by Implicated Antibody, FY2008 through FY2012

Antibody	FY08 No.	FY08 %	FY09 No.	FY09 %	FY10 No.	FY10 %	FY11 No.	FY11 %	FY12 No.	FY12 %	Total No.	Total %
ABO	10	59%	4	33%	2	29%	3	33%	3	38%	22	42%
Multiple Antibodies*	1	6%	2	17%	3	43%	1	11%	2	25%	9	17%
Other**	0	0%	2	17%	0	0%	2	22%	0	0%	4	7%
Fy^a	2	12%	1	8%	0	0%	1	11%	0	0%	4	7%
Jk^b	2	12%	0	0%	1	14%	0	0%	1	13%	4	7%
Kell	2	12%	0	0%	0	0%	1	11%	1	13%	4	7%
Jk^a	0	0%	2	17%	0	0%	0	0%	0	0%	2	4%
c	0	0%	0	0%	0	0%	1	11%	0	0%	1	2%
Js^b	0	0%	1	8%	0	0%	0	0%	1	13%	2	4%
Co^a	0	0%	0	0%	1	14%	0	0%	0	0%	1	2%
Totals	17	100%	12	100%	7	100%	9	100%	8	100%	53	100%

*Multiple Antibodies:

FY2008: anti-C+K+Fy^b+S+N+V+Js^a+Go^a+warm autoantibody.

FY2009: antibody combinations included E+Jk^b, S+Jk^a+Jk^b+K+Fy^a+Fy^b+V+C+N+HTLA.

FY2010: antibody combinations included D+C+K+S, Jk^b+FY^a+C+E+K+Le^a+Le^b, c+E+Jk^b+K+Le^a+panagglutinin+cold agglutinin.

FY2011: anti-Jk^a+c+E+M (warm reacting).

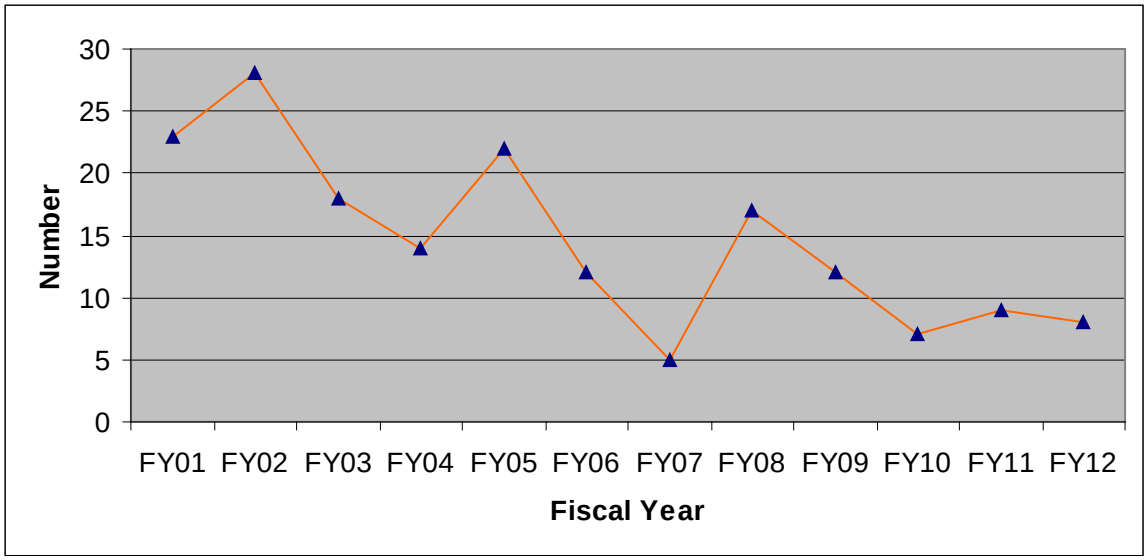
FY2012: antibody combinations included S+E, C+K.

**Other:

FY2009: Includes one report of an unidentified warm autoantibody, and one report of Hyperhemolysis Syndrome. Information about this syndrome has been published.[21]

FY2011: Includes one report of Hyperhemolysis Syndrome, and one report of an unidentified antibody.

Figure 4: Hemolytic Transfusion Reactions, FY2001 through FY2012



[21]Win N, New H, et al. Hyperhemolysis Syndrome in sickle cell disease: case report (recurrent episode) and literature review. Transfusion 2008;48:1231-1238.

In FY2012, there were three reports of fatal hemolytic transfusion reactions due to ABO-incompatible transfusions:

Two of these fatalities were attributed to errors:

- In one case, a phlebotomist collected extra specimens for two patients, anticipating future crossmatch orders for both. The extra specimens were correctly labeled. After receiving crossmatch orders, the phlebotomist switched the specimens and applied the blood bank labels over the existing labels, prior to delivering the specimens to the Blood Bank. As a result, the incorrect blood groups were assigned to both patients, and the group O patient was transfused with an incompatible group A Red Blood Cell (RBC) unit.
- In the second case, a group AB RBC unit, which was correctly labeled for the intended patient, was issued to the Emergency Room (ER), and transfused to a group A patient, who was also in the ER. This error occurred due to failure of ER personnel to properly identify the patient prior to transfusion.

The remaining case illustrates the potential risk associated with ABO-incompatible plasma in plateletpheresis products, when donor ABO antibodies in the transfusion product are incompatible with the patient's red blood cells and are present in sufficiently high titers to cause *in vivo* hemolysis.[22] This case involved transfusion from two group O donors with high-titers of anti-A. Over the last five years there have been two other fatalities due to transfusion of group O apheresis platelets with high-titer blood group antibodies, an anti-A (FY2011) and an anti-B (FY2008). In both of these earlier cases, the recipient's blood group had recently changed following ABO-mismatched hematopoietic stem cell transplants.

In FY2012, there were five reports of non-ABO fatal hemolytic transfusion reactions:

One of the five cases was attributed to a laboratory error. In this case, a positive antibody screen misread as negative resulted in transfusion of three units of incompatible E and/or S positive RBC units. The immediate spin compatibility tests did not detect the incompatibilities. Additionally, the patient's prior records containing the antibody information were misfiled. Records were maintained in a manual record-keeping system.

Two of the remaining four cases involved delayed hemolytic transfusion reactions in patients whose pre-existing antibodies were undetectable prior to transfusion.

The remaining two cases involved emergent transfusions of uncrossmatched RBC units to patients with known pre-existing antibodies. In both cases, there was insufficient time to phenotype units for the corresponding antigens, or to wait for delivery of antigen-negative units from an outside source.

[22] Fontaine MJ, Mills AM, et al. How we treat: risk mitigation for ABO-incompatible plasma in plateletpheresis products. Transfusion 2012;52:2081-2085.

D. Microbial Infection

In FY2012, there were three reported fatalities attributed to microbial infection, compared to four in FY2011. *Babesia microti*, associated with a transfusion of Red Blood Cells, was implicated in one of these fatalities, and *Staphylococcus aureus* and *Serratia marcescens* were implicated, one case each, in platelet transfusion fatalities. Specifically, Apheresis Platelets were associated with the *S. aureus* infection, and the *S. marcescens* infection was associated with a unit of Pooled Platelets (Figure 5).

Babesia accounts for 38% (8/21) of reported deaths due to microbial infection over the previous five fiscal years, followed by *S. aureus*, which accounts for 24% (5/21) (Table 3).

Recent articles provide additional information about transfusion transmitted *Babesia*,[23,24] and bacterial contamination of platelet products.[25,26,27]

During the five-year reporting period, all of the implicated bacteria associated with fatal microbial infections were facultative anaerobes.

Figure 6 shows a downward trend in the number of bacterial infections associated with Apheresis Platelets since FY2001.

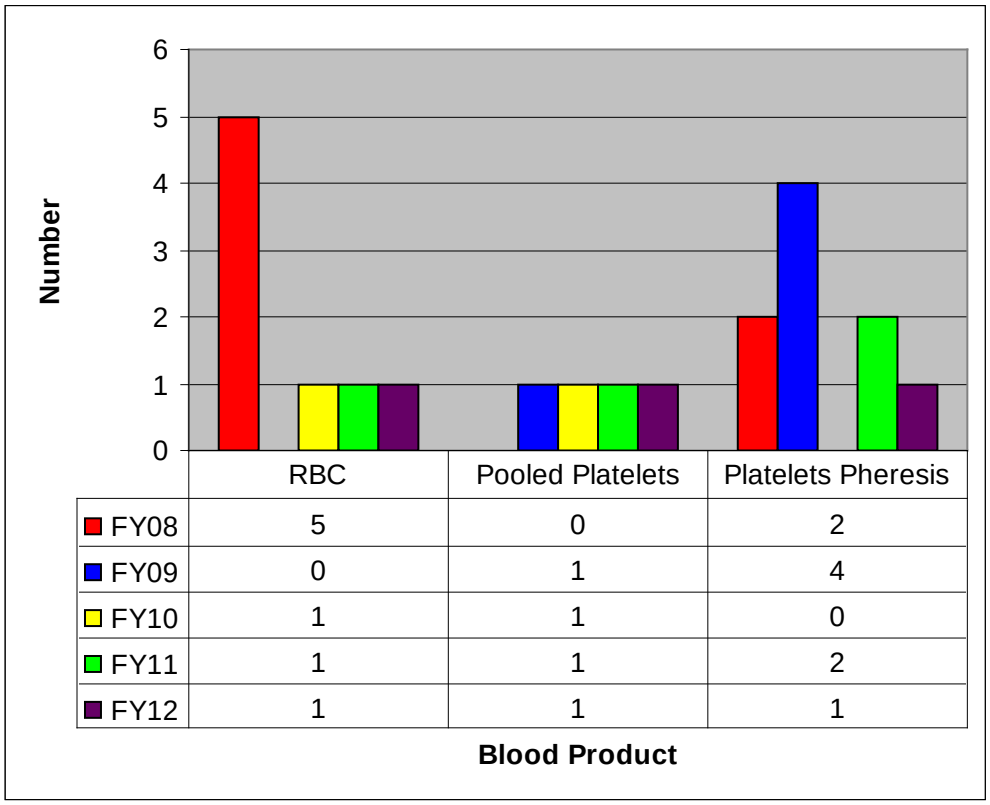
[23] Johnson ST, Van Tassell ER, et al. Babesia microti real-time polymerase chain reaction testing of Connecticut blood donors: potential implications for screening algorithms. Transfusion. doi: 10.1111/trf.12125.
[24] Young C, Chawla A, et al. Preventing transfusion-transmitted babesiosis: preliminary experience of the first laboratory-based blood donor screening program. Transfusion 2012;52:1523-1529..
[25] Rollins MD, Molofsky AB, Nambiar A, et al. Two Septic transfusion reactions presenting as transfusion-related acute lung injury from a split plateletpheresis unit. Crit Care Med 2012;40:2488-2491.
[26] Palavecino EL, Yomtovian RA, Jacobs MR. Bacterial contamination of platelets. Transfus Apher Sci 2010;42:71-82.
[27] Eder AF, Kennedy JM, Dy BA, et al. American Red Cross Regional Blood Centers: Limiting and detecting bacterial contamination of apheresis platelets: inlet-line diversion and increased culture volume improve safety. Transfusion 2009;49:1554-1563.

Table 3: Microbial Infection by Implicated Organism, FY2008 through FY2012

Organism	FY08	FY08	FY09	FY09	FY10	FY10	FY11	FY11	FY12	FY12	Total	Total
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
*Babesia**	5	71%	0	0%	1	50%	1	25%	1	33%	8	38%
Staphylococcus aureus	1	14%	2	40%	0	0%	1	25%	1	33%	5	24%
Escherichia coli	0	0%	0	0%	1	50%	0	0%	0	0%	1	5%
Staphylococcus epidermidis	1	14%	0	0%	0	0%	0	0%	0	0%	1	5%
Morganella morganii	0	0%	0	0%	0	0%	1	25%	0	0%	1	5%
Streptococcus viridans	0	0%	1	20%	0	0%	0	0%	0	0%	1	5%
Streptococcus pneumoniae	0	0%	1	20%	0	0%	0	0%	0	0%	1	5%
Staphylococcus warneri	0	0%	1	20%	0	0%	0	0%	0	0%	1	5%
Klebsiella pneumoniae	0	0	0	0	0	0	1	25%	0	0%	1	5%
Serratia marcescens	0	0	0	0	0	0	0	0	1	33%	1	5%
Total	7	100%	5	100%	2	100%	4	100%	3	100%	21	100%

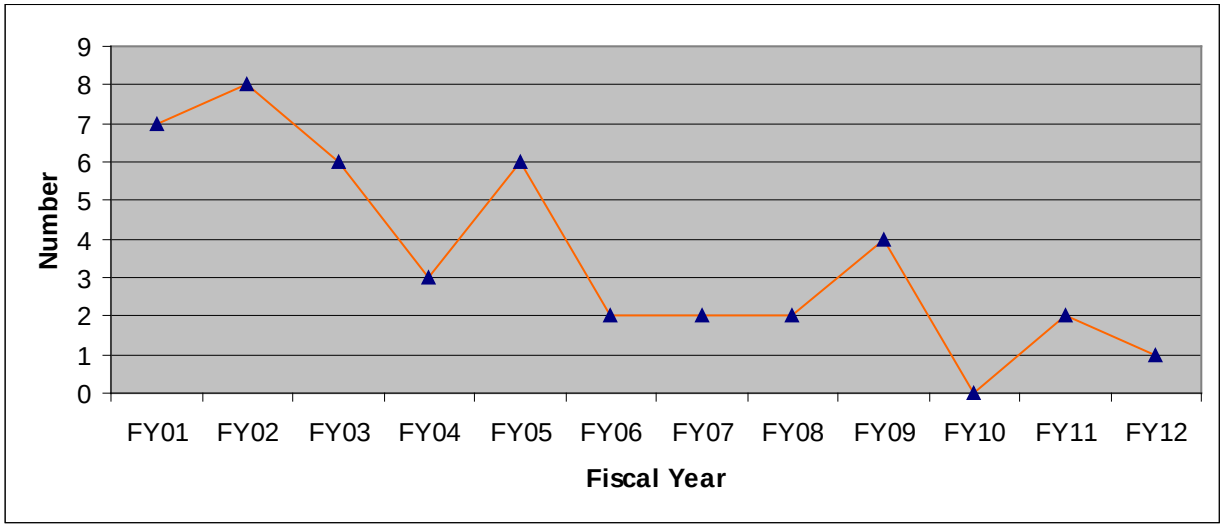
*Seven *Babesia microti* and one probable *Babesia MO-1* species (FY2008)

Figure 5: Microbial Infection by Implicated Blood Product, FY2008 through FY2012



Red Blood Cells microorganisms: *B. microti (7), B. MO1(1)*
Pooled Platelets microorganisms: *S. aureus (1), E. coli (1), S. pneumoniae (1), S. Marcescens (1)*
Platelets Pheresis microorganisms: *S. aureus (4), S. epidermidis (1), M. morganii (1),, S. viridans (1), S. warneri (1), K. pneumoniae (1)*

Figure 6: Bacterial Infection by Apheresis Platelets, FY2001 through FY2012



E. Transfusion Not Ruled Out

As noted above, 27 (36%) of the 74 reported fatalities in FY2012 were cases in which the transfusion could not be ruled out as the cause of the fatality. In these reported fatalities, the reporting facilities were unable to identify a specific complication of transfusion as the cause of death. Often, these patients had multiple co-morbidities, and after review of the investigation documentation, our medical reviewers could neither confirm nor rule out the transfusion as the cause of the fatality (Table 4). Therefore, we did not include these 27 reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities).

F. Not Transfusion Related

After reviewing the initial fatality reports and the investigation documentation, we categorized 9 (12%) of the 74 reported fatalities as "Not Transfusion Related." Our medical reviewers concluded that, while there was a temporal relationship between transfusion and subsequent death of the recipient, there was no evidence to support a causal relationship (Table 4). Thus, we did not include these reported fatalities in the analysis in Sections II.A through II.D (transfusion-related fatalities).

Table 4: Fatalities Not Related to Transfusion or Transfusion Not Ruled Out, FY2008 through FY2012

	FY08	FY09	FY10	FY11	FY12
Transfusion Not Ruled Out	8	22	24	28	27
Not Transfusion Related	18	8	7	11	9
Totals	26	30	31	39	36

G. Post-Donation Fatalities

In FY2012, there were 12 reports of fatalities following Source Plasma donation, and two reports of fatalities following Whole Blood donation. In 9 of the 12 Source Plasma donor deaths, and both Whole Blood donor deaths, although the donations could not be definitively ruled out as being implicated in the donors' deaths, our medical reviewers found no evidence to support a causal relationship between the donations and subsequent death of the donors.

In 3 of the 12 reports of fatalities following Source Plasma donation in FY2012, the donations were definitively ruled out as being implicated in the death of the donors. In each of these cases, there was clear evidence showing the cause of death was unrelated to the donation.

Over the five-year reporting period there were four Source Plasma donations (three FY2012 reports and one FY2011 report), and one Whole Blood donation (FY2011) in which the donations were definitively ruled out as the cause of death. For the remaining cases, our medical reviewers concluded that, while there was a temporal link between the donations and the fatalities, there was no evidence to support a causal relationship between the donations and subsequent death of the donors (Table 5 and Figure7).[28]

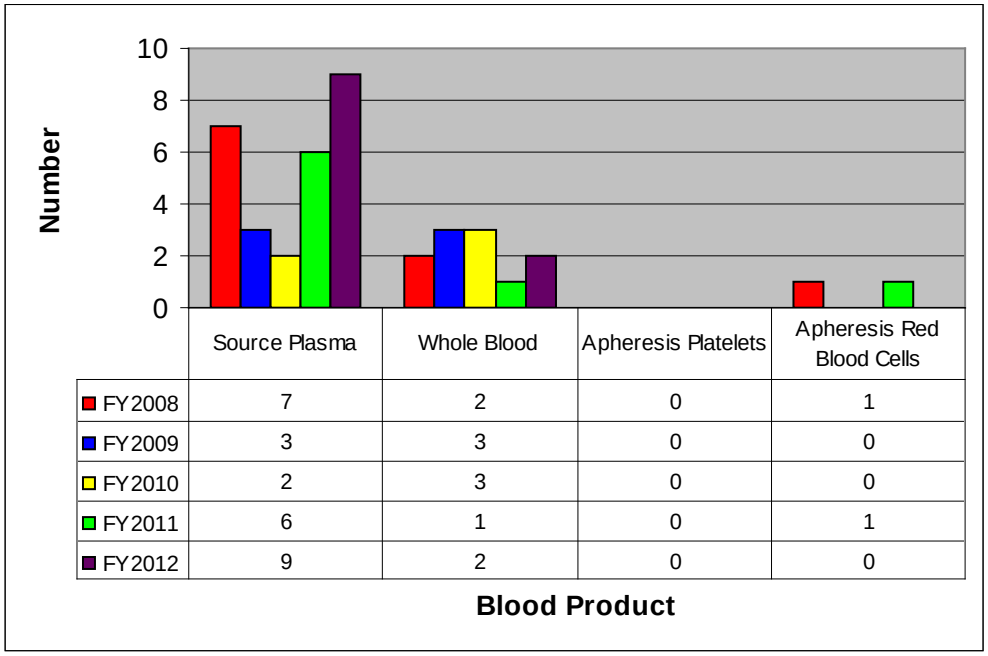
Over the last three fiscal years, there has been an upward trend in the number of reported fatalities following Source Plasma donation. The FDA will continue to monitor and assess this trend, and has encouraged Industry to do the same.

Table 5: Post-Donation "Not Ruled Out" Fatality Reports by Donated Product, FY2008 through FY2012[28]

Donated Product	FY08	FY09	FY10	FY11	FY12
Source Plasma	7	3	2	6	9
Whole Blood	2	3	3	1	2
Apheresis Platelets	0	0	0	0	0
Apheresis Red Blood Cells	1	0	0	1	0
Total	10	6	5	8	11

[28] In previous fiscal years, discussion of the post-donation fatality reports has included all of the reported donor fatalities; in the current report, the reported donor fatalities in which the donation has been ruled out as the cause of death are not included in the discussion or representative data charts.

Figure 7: Post-Donation "Not Ruled Out" Fatality Reports, FY2008 through FY2012[28]



	Source Plasma	Whole Blood	Apheresis Platelets	Apheresis Red Blood Cells
FY2008	7	2	0	1
FY2009	3	3	0	0
FY2010	2	3	0	0
FY2011	6	1	0	1
FY2012	9	2	0	0